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COMMENTS AT THE EPA PUBLIC SCIENCE MEETING ON RDX

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Cross-cutting concerns

1) Use of outdated and problematic Preamble
2) Quantification of the Suggestive Endpoint
3) Choice of BMD 1%
4) Lack of clear criteria for evaluating study quality

Use of a Outdated and Problematic Preamble

- Preamble was reviewed in 2015 by two Chemical Assessment Advisory Committees (Ammonia, Trimethylbenzenes). Reports sent to EPA in August and September 2015.
  - "The SAB recommends that the agency take measures to ensure that the Preamble in this and future assessments be structured so that it refers the reader to the appropriate guidance and cannot be construed to contradict policy by over summarizing existing guidance."
  - "Many of the components of such protocols are described in the Preamble of the ammonia assessment, but the extent and mechanisms for their application to the ammonia assessment are not sufficiently clear."
  - "Since the Preamble is a complex, "stand alone" document, at some future date (not for this ammonia assessment) it would be advisable to have it separately examined and reviewed in detail."

- Preamble should be removed from this draft and all future assessments until a robust review is completed. In place of the preamble, within the RDX assessment, EPA should reference specific guidance (not general preamble discussion).

Quantitation of the Suggestive Cancer Endpoint

- 2005 Cancer Guidelines state: "When there is suggestive evidence, the Agency generally would not attempt a dose-response assessment, as the nature of the data generally would not support one; however, when the evidence includes a well-conducted study, quantitative analyses may be useful for some purposes, for example, providing a sense of the magnitude and uncertainty of potential risks, ranking potential hazards, or setting research priorities."

- RDX draft states (page 1-25): "Considering the data from these studies, along with the uncertainty associated with the suggestive nature of the weight of evidence, ***quantitative analysis of the tumor data may be useful for providing a sense of the magnitude of potential carcinogenic risk***." (emphasis added)
  - Draft charge is silent on appropriate use

- Charge for peer reviewers should include a question to peer reviewers asking them to comment on the strength of the evidence and recommended appropriate uses for any quantified value.

Choice of BMD 1%

- EPA BMD Technical Guidance (2012):
  - For reporting purposes, it is recommended that the BMD corresponding to 10% extra risk always be presented.

    Can serve as a comparison across chemicals and for hazard ranking
  - Is not a default, other values can be used based on statistical and biological considerations
- EPA has chosen a 1% level for convulsions, noting it is severe
  - EPA states in multiple places "there is evidence of an association" between convulsions and mortality
  - However, deeper evaluation shows (page 1-7 and elsewhere) that pre-term death did not occur in all animals that convulsed. The relationship is "not clear" (page 1-72).

- Provide further justification for "severity" of convulsions.
- Provide a clear table in the dose-response chapter showing the BMD and BMDL levels for 1%, 5% and 10%

Lack of Clear Criteria for Evaluating Study Quality

- Page LS-8 notes some study considerations and notes studies evaluated consistent with the Preamble
  - Approach is vague. Preamble presents multiple options, none of which are transparently adopted
  - Table LS-3 is missing critical features (e.g., consideration of route of exposure)
  - Any further discussion of study quality is absent
- No clear, consistent, and transparent evaluation of the quality of individual studies is provided
- EPA chose a gavage study over a dietary study without sufficient justification (other Federal Agencies have relied on the oral study)
  - ES-5 notes that gavage may induce convulsions due to bolus dose, gavage study introduces uncertainty

- EPA should provide clear criteria for study evaluation and should transparently benchmark each study against these criteria.
- Charge for peer reviewers should include a clear question taking comment on the choice of a gavage study over a dietary study. This should be based on study quality considerations, not considerations of outcomes.